CHAPTER 7

- The Intranasal route of administration.
- Classes of medicinal agents applied by this route.
- Factors affecting the utility of this route and applications.

➢Introduction:

- Administration of drug through nasal route is referred as **Nasal drug delivery system.**

- Nasal mucosa has been considered as a potential administration route to achieve **faster** and **higher level of drug absorption**.

- It is an **ideal alternative** to the parenterals for systemic drug delivery

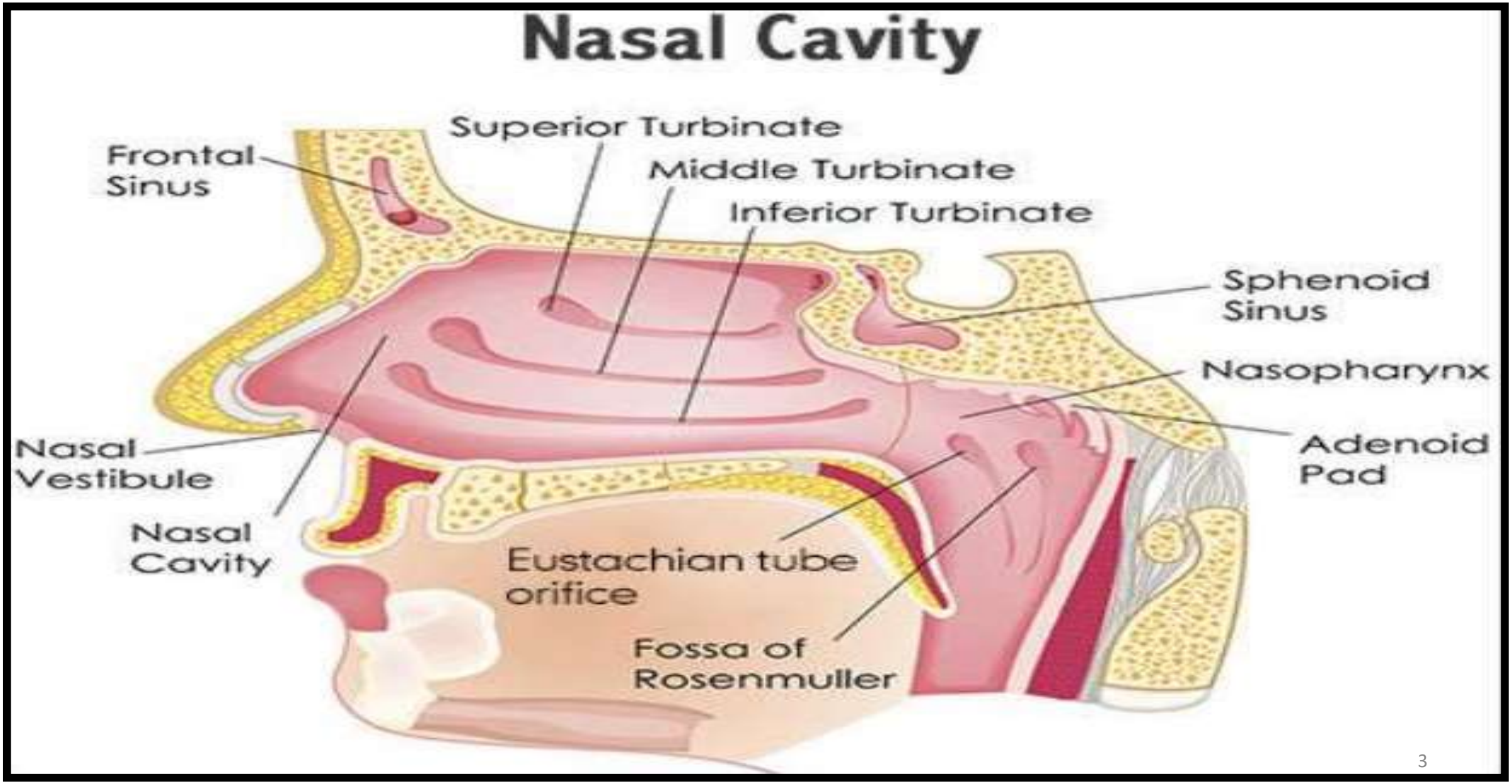
- Drugs are administered to the nasal cavity for:

a) Local and systemic action

b) Vaccine delivery

c) Possible direct nose - brain delivery.

Anatomy and Physiology of Nose



- The nasal cavity is run from the nasal vestibule to the nasopharynx which has depth of approximately 12-14 cm and it is about 60 mm in length.
- **The nasal cavity is d**ivided into two halves by the **nasal septum** and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril.
- **Three main regions** of the nasal cavity: The nasal vestibule, the respiratory region and the olfactory region.
- The **submucosal zone** of the nasal mucosa directly connects to the systemic circulation → A**voids 1st - pass metabolism**.
- The lateral walls of the nasal cavity includes **a folded structure → enlarges** the **surface area** in the nose to about 150 cm2 .
- This folded structure includes three turbinates: The superior, the median and the inferior → **Increases the surface area of absorption**.

- **The nasal cavity is covered with a mucous membrane** which can be divided into:
  - ✓ Non-olfactory epithelium area and
  - ✓ Olfactory epithelium areas (includes the nasal vestibule and respiratory region).
- **Nasal blood flow→** external and internal carotid arteries.
- **Nasal secretions** (1500-2000 ml/day) → Goblet cell, nasal glands, transudate from plasma & lacrimal glands.
  - **Composition**: 95% water, 1-2% salt, 2-3% mucin in trace amount Na, K, Ca, Albumin also present.
- **Nasal enzymes**: Monooxygenase, lactate dehydrogenase, oxidoreductase, phosphates , hydrolases, esterases, etc.
- **Nasal pH**:
  - ✓5.5-6.5(adults)
  - ✓5.0-6.7(infants & child)

➢ADVANTAGES

1. Drug degradation is absent.
2. Hepatic first – pass metabolism is absent.
3. Rapid drug absorption (highly vascularized mucosa).
4. Quick onset of action.
5. The bioavailability of larger drug molecules can be improved by means of absorption enhancers or other approach.
6. Better nasal bioavailability for smaller drug molecules.
7. Drugs which can not be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system.
8. Convenient route when Compared with parenteral route for long term therapy. (Ease of administration, non-invasive, self administration).

➢Disadvantages :

1.The absorption enhancers used to improve nasal drug delivery system may have **histological toxicity** which is not yet clearly established.

2.Absorption surface area is **less** when compared to GIT.

3.Nasal **irritation**.

4.There is a **risk of local side effects** and irreversible damage of the cilia on the nasal mucosa.

Therapeutic class of drugs

1. b2 adrenergic agonists
2. Corticosteroids
3. Antiviral
4. Antibiotics
6. More recently, vaccines
5. Antifungal.
6. Hormones→ insulin, Vassopressin, ACTH

DOSAGE FORMS

1.Liquid Formulation
2.Powder Formulation
3.Nasal Gel
4.Nasal Drop
5.Nasal Spray

Application

1.Delivery of non-peptide pharmaceuticals.
2.Delivery of peptide-based pharmaceuticals
3.Delivery of Drugs to Brain through Nasal Cavity
4.Delivery of Vaccines through Nasal Route
5.Delivery of diagnostic drugs

➢**Three classes of medicinal agents are applied by the nasal route:**

1.Drugs for the alleviation of nasal symptoms; drugs that are inactivated in the gastro-intestinal

2.Tract following oral administration and where the route is an alternative to injection.

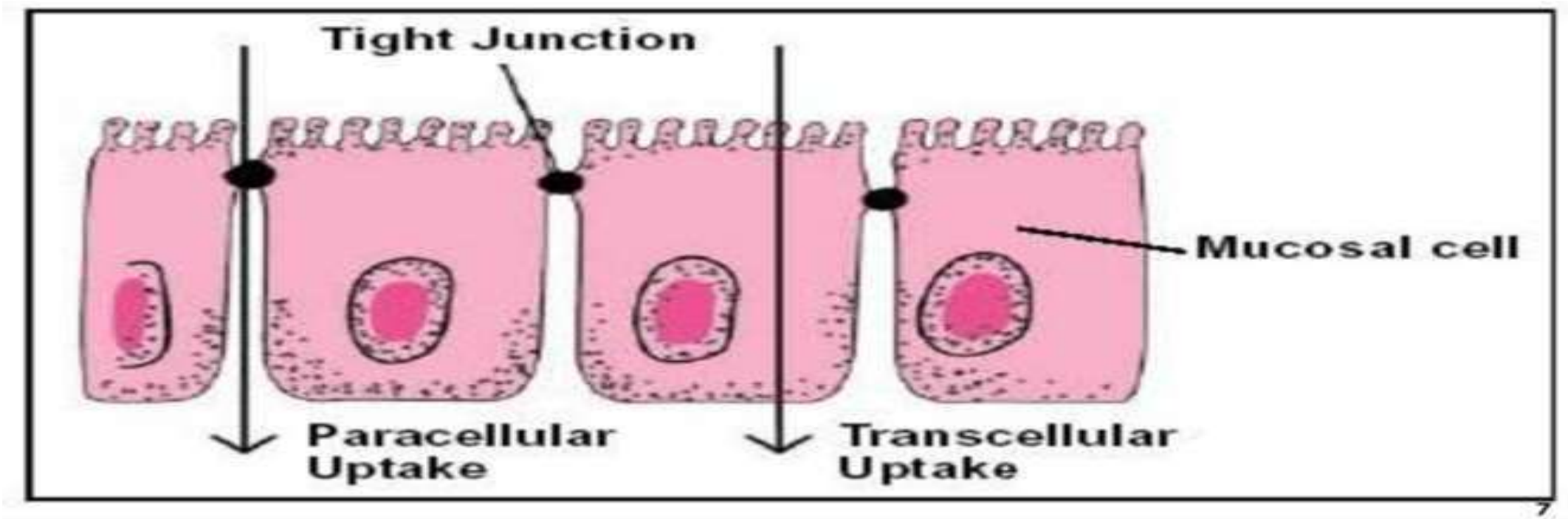
3.And vaccines.

➢ MECHANISM OF ABSORPTION

- The absorbed drug from the nasal cavity must pass through the mucus layer.
- It is the first step in absorption.
- **Two mechanisms are found: (as known)**

1.Transcellular process

2.Paracellular process:



➢ MUCOCILIARY CLEARANCE

- It is a preventive function.
- Prevents the entry of hazardous particles.
- When the drugs adhere to the nasal mucosa, they eventually goes into nasopharynx and lead towards GIT.

- This clearance of mucus and the adsorbed/dissolved substances into GIT called as **Mucocilliary clearance (MCC).**

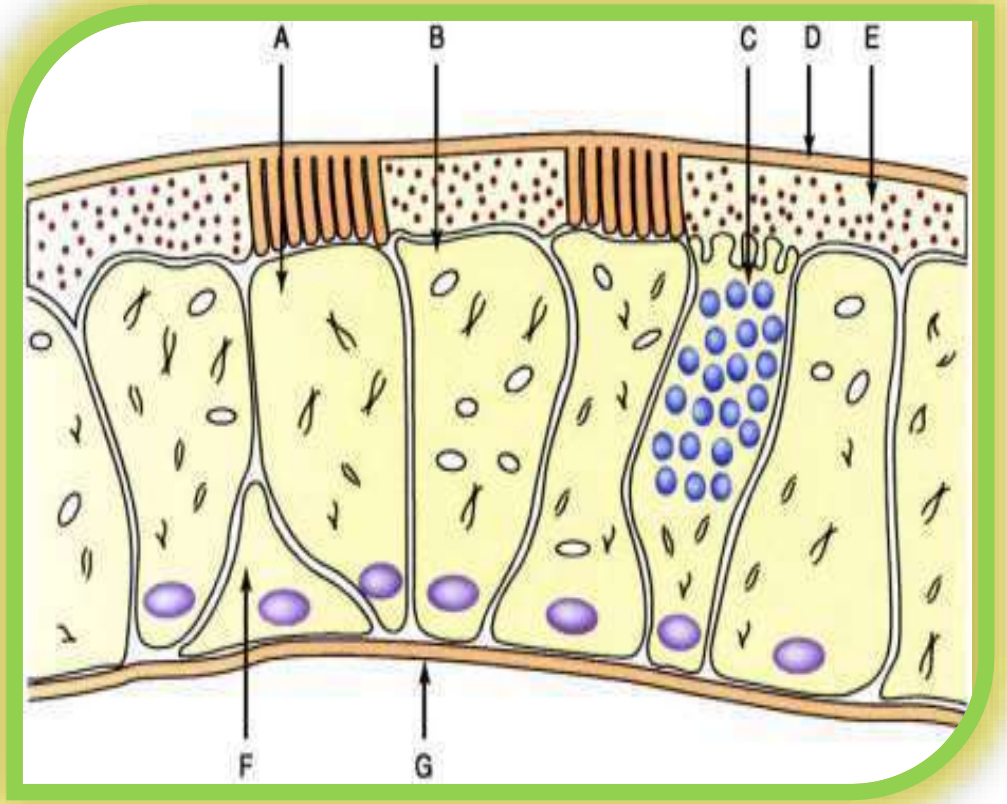


Fig- Cell types of the nasal epithelium

A-Ciliated cells
B-Nonciliated cells
C-Goblet cells
D-Mucus layer
E-Sol layer
F-Basal cells
G-Basement membrane.

➢ BARRIERS TO NASAL ABSORPTION

○ Low Bioavailability:

- Due to **Low membrane permeability** (limiting factor for high M.wt polar drugs like protein and peptides).

○ Low Membrane Transport:

- Rapid clearance of administered formulation due to mucociliary clearance mechanism (MCC).
- Ex: Liquid and powder formulation shows rapid clearance.

○ Enzymatic Degradation:

- Enzymatic degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier.
- Degradation of protein and peptides by Exopeptidase and Endopeptidase.

➢STRATEGIES TO IMPROVE NASAL ABSORPTION:

1

- To improve the nasal residence time.
- Various mucoadhesive polymers→ Increase in the higher local drug conc. in the mucous lining of the nasal mucosa→ Increase nasal residence time.
- E.g. MC (Methyl Cellulose), CMC (Carboxy Methyl Cellulose), PAA (Poly Acrylic Acid).

2

- To enhance nasal absorption→ Mechanisms: (it should be achieved by)
- Increased drug solubility
- Decreased mucosal viscosity.
- Decrease enzymatic degradation.
- Increased paracellular transport.
- Increased transcellular transport.

3

- To modify drug structure to change physiochemical properties→ Prodrug and particulate drug delivery.

➢Strategies To Improve Nasal Absorption

1.*Nasal Enzymes Inhibitors:*

e.g.:- peptidases, proteases, tripsin, aprotinin, borovaline, amas-tatin, bestatin and boroleucin inhibitors.

2.Formulation Design:

3. Modifying drug structure:

e.g.:- chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin.

4.Prodrug approach:

e.g.:- peptides like angiotensin II, bradykinin, caulein, carnosine, enkephalin, vasopressin and calcitonin.

5.Particulate drug delivery:

6.Absorption Enhancers:

❖Mechanism of Penetration Enhancers:

1.Inhibit enzymatic activity.

2.Reduce mucus viscosity.

3.Reduce **MCC.**

4.Open tight junctions.

5.Solubilize the drug.

❖Ideal Properties:

1.It should increase the absorption of the drug.

2. It should not cause permanent damage or alteration to the tissue.

3. It should be non irritant and nontoxic.

4. It should be effective in small quantity.

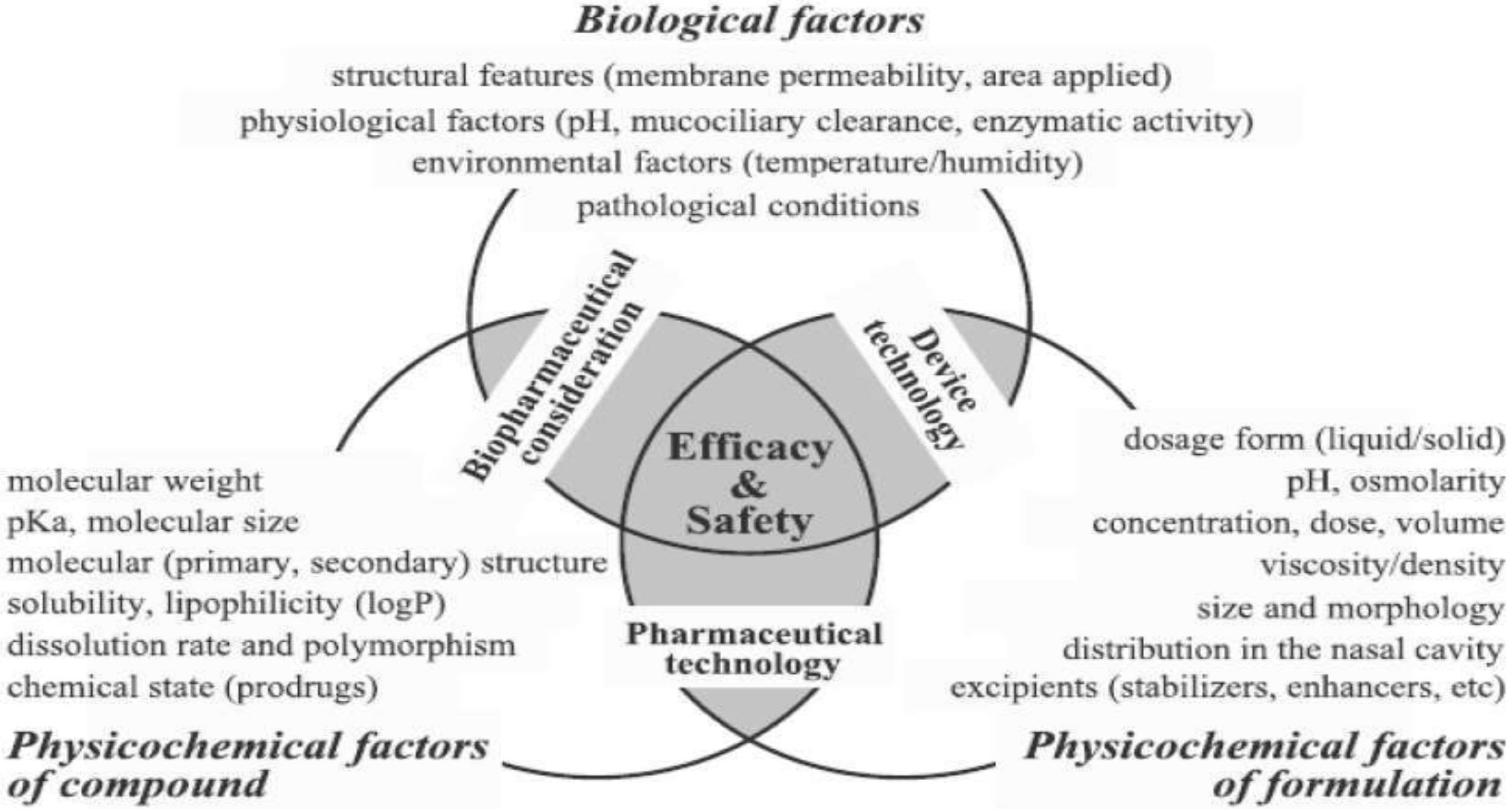
5. The enhancing effect should occur when absorption is required.

6. The effect should be temporary and reversible.

7. It should be compatible with other excipients.

❖ Classification of penetration enhancer

Type	Examples
Surfactants	Sodium dodecyl sulphate, Polyoxyethylene-9-lauryl ether, Saponin
Complexing and chelating agents	EDTA, Salicylates
Cyclodextrins and derivatives	α-, β-, γ-cyclodextrin, DMβ-cyclodextrin, HPβ-cyclodextrin
Bile salts	Sodium taurocholate Sodium glycocholate Sodium deoxycholat Fusidic acid derivatives
Fatty acid salts	Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)
Dry microspheres	Degradable starch microsphere Dextran microsphere


Biological factors
structural features (membrane permeability, area applied)
physiological factors (pH, mucociliary clearance, enzymatic activity)
environmental factors (temperature/humidity)
pathological conditions
Biopharmaceutical consideration
Device technology
Efficacy & Safety
Pharmaceutical technology
molecular weight
pKa, molecular size
molecular (primary, secondary) structure
solubility, lipophilicity (logP)
dissolution rate and polymorphism
chemical state (prodrugs)
Physicochemical factors of compound
dosage form (liquid/solid)
pH, osmolarity
concentration, dose, volume
viscosity/density
size and morphology
distribution in the nasal cavity
excipients (stabilizers, enhancers, etc)
Physicochemical factors of formulation

➢FACTORS AFFECTING ABSORPTION

A. Physicochemical factors:

1.Chemical form:

- The form of a drug can be important in determining absorption.
- Example: **carboxylic acid esters of L-Tyrosine** >> L-Tyrosine (Nasal absorption).

2. Polymorphism:

- Polymorphism affects → the dissolution rate, solubility of drug → and thus their absorption through biological membranes.

3. Molecular Weight:

✓The nasal absorption of drugs decreases as the molecular weight increases.

4. Solubility and Dissolution Rate:

- Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions.
- The particles deposited in the nasal cavity need to be dissolved prior to absorption.

5. Lipophilicity :-

- Absorption of drug through nasal route is dependent on the lipophilicity of drugs.
- E.g. Alprenolol and Propranolol which are lipophilic, has greater absorption than that of hydrophilic Metoprolol.

B. FORMULATION CONSIDERATION

1.Volume :

- Nasal formulation are generally administered in small volumes. in the range 25-200 μ L. (Approximately 100 μL the most common dose volume).

2 Particle size:

- 10 -20μm - deposited in nasal cavity.
- Less than 2 μm - retained in the lungs.
- Greater than 20- they are exhaled.

3. Isotonicity→ OSMOTIC AGENT

4.pH of the formulation → BUFFERS

•***pH It is important as..***

•To avoid irritation of nasal mucosa.

•To allow drug to be available in unionized form for absorption.

•To prevent growth of the bacteria in nasal passage.

•To sustain normal physiological ciliary moments.

•pH should be optimum for maximum absorption.

• Nonionized lipophilic form crosses the nasal epithelial barriers via transcellular route and hydrophilic ionized form passes through the aqueous paracellular route.

•E.g. Decanoic acid shows maximum absorption at pH 4.5. Beyond this it decreases as solution becomes more acidic or basic.

•**Note: Nasal pH:**

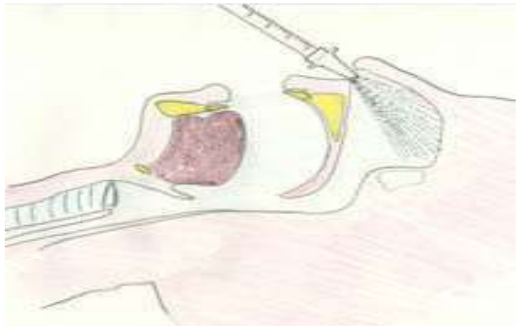
- 5.5 - 6.5 (adult)
- 5.0 - 6.7(infants)

5. Drug concentration:

•The absorption of drug through nasal route is increased as concentration is increased.

• E.g. 1-tyrosine shows increased absorption at high concentration in rate.

6. Nasal mucosal surface area coverage:



•Larger surface area delivery = higher bioavailability.

•Atomization → higher bioavailability than either spray or drops.

•For this reason, nasal pharmaceuticals come with atomized drug delivery systems.

7. Drugs distribution and deposition :

•The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition.

•The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug.

8. The excipients:

* Should be carefully selected so as to avoid damage to the mucoepithelial layers and to sustain normal physiological ciliary movement.

1) BUFFERS
2) OSMOTIC AGENTS
3)GELLING AGENTS
4)SOLUBILISERS
5) PRESERVATIVES
6)ANTIOXIDANTS
7)HUMECTANTS
8)ABSORPTION ENHANCERS
9)SURFACTANTS
10)CHITOSAN
11)CYLODEXTRINS
12)COMPLEXING AGENTS

1.HUMECTANTS

•Adequate intranasal moisture is required→

humectants are added (to prevent dehydration).

•Prevent nasal irritation.

•The commonly used humectants are

- Glycerin
- Sorbitol
- Mannitol

2. OSMOTIC AGENTS

•The osmolarity of the dosage form affect the nasal absorption of the drug.

•The higher concentration of drug not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium.

•The commonly used osmotic agents are:

- Sodium Chloride.
- Sodium sulfite.
- Sodium acid phosphate.

3. SOLUBILIZERS

•Aqueous solubility of drug is always a limitation for nasal drug delivery of dosage form.

•**Commonly used solubilizers are:**

- Glycols
- Small quantities of alcohol.
- Transcutol(diethylene glycol monoethyl ether).
- Medium chain glycerides.
- Labrasol (saturated polyglycolysed C8-C10 glycerides).
- Surfactant.
- Cyclodextrine (B-cyclodextrin).

4.GELLING/VISCOSIFYING AGENTS/GEL FORMING CARRIER

- Increasing solution viscosity → Prolonging the therapeutic effect of nasal preparations.
- Highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance → alter the permeability of drug →increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation.
- Commonly used gelling agents are→ Carbopol, Cellulose agents, Starch and Dextran.

5.ABSORPTION ENHANCERS

- Unlike the most small drug molecules, some drugs and peptides do no cross the nasal membrane efficiently.
- The nasal mucosa is almost impermeable to molecular size >1000 Dalton.
- The low nasal membrane permeability is due to:
    1. Molecular Size.
    2. Lack Of Lipophilicity.
    3. Enzymatic Degradation, Chitosan, etc.

6.ANTIOXIDANTS

- Usually antioxidants→ do not affect drug absorption or cause nasal irritation.
- Chemical / Physical interaction of antioxidant with drug and excipients should be considered during formulation development.
- Commonly used antioxidants are
    - Sodium Metabisulfite.
    - Sodium Bisulfite.
    - Butylated Hydroxytoluene.
    - Tocopherol.

7. PRESERVATTVES

- Commonly Used Preservatives
    - Parabens
    - Benzolkonium Choride
    - Phenyl Ethyl Alcohol
    - Benzoyl alcohol
    - **Mercury containing preservatives are not used.**

C. The biological and physiological conditions

1. Membrane permeability

•The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having lower membrane permeability.

2.Vascularity

3. Mucus flow rate.

4.Drug metabolism in the respiratory tract and reduction of systemic effect.

(peptides and proteins have lower bioavailability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier).

5.Protein binding.

6.Mucociliary Clearance → drug residence time.

7.Pathological conditions→ allergic rhinitis and cold → hyper secretion, itching and ….etc.

Various Nasal Drug Delivery Formulations


Nasal spray


Nose drops


Metered dose spray


Saturated cotton pledge


Mucosal atomizer device


Nasal gels


Nasal ointments


Mucosal atomization device


Nebulizer


Nasal powder

➢ MARKETED PREPARATIONS

MARKETED FORMULATION	ACTIVE INGREDIENT
Otrivine adult nasal drop	Xylometazoline hydrochloride 0.1w /v
Dymista nasal spray , suspension	Azelastinehydrochloride, fluticasoneproprionate
Imitrex nasal spray	sumatriptan
Stimate nasal spray	Desmopressin acetate
Miacalcic nasal spray	Calcitonin
Vibrocil gel	Phenylephrine, dimethindene maleate
Astelin nasal spray	Azelastine hydrochloride